

In the Claims.

Please amend the claims as shown below. This listing of claims will replace all prior versions and listings of the claims in this application.

1-29 (Cancelled).

30. (New) Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a target for the identification of agents which modulate DNA replication.

31. (New) Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a target for the inhibition of cell proliferation.

32. (New) A screening method for the identification of agents which modulate DNA replication wherein the screening method comprises the use of Ciz1 nucleotide or polypeptide sequence or any fragment or variant thereof.

33. (New) The screening method according to claim 32 wherein said method comprises detecting or measuring the effect of an agent on a nucleic acid molecule selected from the groups consisting of:

- a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of Figures 14, 15, or 21;
- b) a nucleic acid molecule which hybridises to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;
- c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and a candidate agent to be tested; and
- d) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence.

34. (New) The method according to claim 33 wherein said nucleic acid molecule is modified by deletion, substitution or addition of at least one nucleic acid residue of the nucleic acid sequence.

35. (New) The screening method according to claim 32, wherein said method comprises one or more of the following steps:

(i) forming a preparation comprising a polypeptide molecule, or an active fragment thereof, encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of Figures 14, 15, or 21;

b) a nucleic acid molecule which hybridizes to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;

c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and a candidate agent to be tested; and

d) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence; and

(ii) detecting or measuring the effect of the agent on the activity of said polypeptide.

36. (New) The method according to claim 35 wherein said polypeptide is modified by deletion, substitution or addition of at least one amino acid residue of the polypeptide sequence.

37. (New) The method according to claim 32 wherein said screening method is a cell-based screening method.

38. (New) The method according to claim 37 wherein the cell naturally expresses the Ciz1 polypeptide.

39. (New) The method according to claim 37 wherein the cell is transfected with a nucleic acid molecule encoding Ciz 1 or a fragment or variant thereof.
40. (New) An agent selected from the group consisting of: polypeptide or nucleic acid probe; polypeptide; peptide; aptamer; chemical; antibody; nucleic acid which binds to the Ciz1 nucleotide or polypeptide sequence, and any fragment or variant thereof which modulates DNA replication.
41. (New) An agent according to claim 40 wherein said agent is an antibody molecule and binds to any of the sequences represented by Figures 16, 17, or 20.
42. (New) An antibody molecule according to claim 41 wherein said antibody is a monoclonal antibody.
43. (New) An agent according to claim 40 wherein said agent is an anti-sense nucleic acid molecule or RNAi which binds to and thereby blocks or inactivates the mRNA sequence of Ciz1 or any fragment or variant thereof.
44. (New) An agent according to claim 43 wherein said agent binds to any part of the sequences illustrated in Figures 14, 15, or 21 or in part (i) b-d of claim 32.
45. (New) An agent according to claim 43 wherein said agent binds to mRNA sequences created at alternatively spliced sites.
46. (New) An agent according to claim 45 wherein said agent binds to the mRNA sequence created by alternative splicing at exon 14 of Ciz 1.
47. (New) An agent according to claim 45 wherein said agent binds to the mRNA sequence created by exon skipping of exon 4 of Ciz 1.

48. (New) A vector for delivering an antisense or RNAi molecule to a cell wherein the vector includes an expression cassette comprising the nucleotide sequence selected from the group consisting of:

- a) the nucleic acid sequence which encodes Ciz1 amino acid sequence as shown in Figs 14, 15, and 21;
- b) a nucleic acid molecule which hybridizes to the nucleic acid sequence of (a);
- c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and any sequence which is complimentary to any of the above sequences; and
- d) a nucleic acid sequence that encodes Ciz1 pre-mRNA (i.e., the genomic sequence).

49. (New) A vector according to claim 48 wherein the expression cassette is transcriptionally linked to a promoter sequence.

50. (New) Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as diagnostic, prognostic or therapeutic reagent.

51. (New) A diagnostic method for the identification of proliferative disorders comprising detecting the presence or expression of the Ciz 1 gene, Ciz1 splice variants and mutations in the genomic or protein sequence thereof.

52. (New) A diagnostic method according to claim 51 wherein said method comprises one of more of the following steps:

- (i) contacting a sample isolated from a subject to be tested with an agent which specifically binds a polypeptide with Ciz 1 activity or a nucleic acid molecule encoding a polypeptide with Ciz 1 activity;
- (ii) detecting or measuring the binding of the agent on said polypeptide or nucleic acid in said sample;

- (iii) use of reverse-transcribed PCR or real-time PCR to monitor Ciz1 and Ciz1 isoform expression and to measure expression levels;
- (iv) measuring the presence of nucleic acid or amino-acid mutations based on altered conformational properties of the molecule; and
- (v) sequence determination, optionally comprising an array based sequencing chip.

53. (New) A pharmaceutical comprising an agent according to claim 40 in association with a pharmaceutically acceptable carrier, excipient or diluent.

54. (New) A pharmaceutical comprising a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof which binds to Ciz 1 alternate splice variants, in association with a pharmaceutically acceptable carrier, excipient or diluent.

55. (New) An agent according to claim 40 for use as a medicament.

56. (New) Ciz 1 nucleotide or polynucleotide sequence, or any fragment or variant thereof for use as a medicament.

57. (New) Use of an agent according to claim 40 for the manufacture of a medicament for the treatment of proliferative disease.

58. (New) Use of Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof for the manufacture of a medicament for the treatment of proliferative disease.

59. (New) Use according to claim 57 or claim 58 wherein said proliferative disease is cancer.

60. (New) Use according to claim 59 wherein said cancer is a paediatric cancer and is selected from the group consisting of; retinoblastoma, neuroblastoma, Burkitt lymphoma, medulloblastoma, and Ewings Sarcoma family tumours (ESFTs),
61. (New) Use according to claim 59 wherein said cancer is a carcinoma, adenocarcinoma, lymphoma or leukemia.
62. (New) Use according to claim 57 or 58 wherein said disease is liver, lung or skin cancer or metastasis.
63. (New) A method to treat a proliferative disease comprising administering to an animal, an agent according to claim 40.
64. (New) A kit comprising an agent according to claim 40.
65. (New) A kit comprising Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof which binds to Ciz 1 alternate splice variants.